NAD BIOSYNTHESIS AND PRECURSORS FOR THE TREATMENT AND PREVENTION OF CANCER AND PROLIFERATION

This application is a national stage filing under 35 U.S.C. § 371 of international application PCT/US2013/064154, filed Oct. 9, 2013, entitled "NAD Biosynthesis and Precursors for the Treatment and Prevention of Cancer and Proliferation," which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Ser. No. 61/711,552, entitled "Treatment of Age-Related and Mitochondrial Diseases by Inhibition of HIF-1α Function," filed on Oct. 9, 2012, U.S. Provisional Application Ser. No. 61/832,414, entitled "NAD Biosynthesis and NAD Precursors for the Treatment of Disease," filed on Jun. 7, 2013, and U.S. Provisional Application Ser. No. 61/832,203, entitled "NAD Biosynthesis and Precursors for the Treatment and Prevention of Cancer and Proliferation," filed on Jun. 7, 2013, the entire contents of each of which are herein incorporated by reference in their entireties.

GOVERNMENT INTEREST

This invention was made with Government support under National Institutes of Health Grant AG028730. The Government has certain rights in this invention.

FIELD OF THE INVENTION

The invention relates to methods for treatment and prevention of diseases or disorders associated with mitochondrial dysfunction by administering inhibitors of HIF1-α and/or agents that increase levels of NAD+. The invention relates to methods for treatment and prevention of cancer by administering agents that increase levels of NAD+.

BACKGROUND

Aging is characterized by a progressive decline in cellular and tissue homeostasis leading to a variety of age-related diseases that limit lifespan. Although improvements in sanitation, diet and medicines over the past 100 years have produced dramatic improvements in human health, maximum human lifespan has not changed. The inability to impact the maximal lifespan is due, in large part, to a limited understanding of why aging occurs and what genes control these processes.

Mitochondria are highly dynamic organelles that move throughout the cell and undergo structural transitions, changing the length, morphology, shape and size. Moreover, mitochondria are continuously eliminated and regenerated in a process known as mitochondrial biogenesis. Over the past 2 billion years, since eukaryotes subsumed the α-proteobacterial ancestor of mitochondria, most mitochondrial genes have been transferred to the nuclear genome, where regulation is better integrated. However, the mitochondrial genome still encodes rRNAs, tRNAs, and 13 subunits of the electron transport chain (ETC). Functional communication between the nuclear and mitochondrial genomes is therefore essential for mitochondrial biogenesis, efficient oxidative phosphorylation, and normal health. Failure to maintain the stoichiometry of ETC complexes is exemplified by mitochondrial disorders such as Leber's hereditary optic neuropathy (LHON), mitochondrial encephalomyopathy, lactic acidosis and stroke like episode syndrome (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), and Leigh Syndrome.

One of the most conserved and robust phenomena in biology, in organisms as diverse as yeast and humans, is a progressive decline in mitochondrial function with age leading to a loss of cellular homeostasis and organismal health. In mammals, there is a large body of evidence implicating mitochondrial decline in aging and age-related diseases, including type II diabetes, Parkinson's disease, Alzheimer's disease, sarcopenia, lethargy, frailty, hepatic steatosis and obesity. For example, mice with mutations that impair the proofreading capacity of the mitochondrial DNA polymerase gamma (Poly) exhibit a premature aging phenotype. Conversely, targeting peroxisomal catalase to mitochondria (mCAT) extends mouse lifespan. Recently, telomere erosion in mice was found to disrupt mitochondrial function but the underlying mechanism has not yet been established. Despite the apparent importance of mitochondrial decline in aging and disease, there is considerable debate about its underlying causes.

Deregulation of mitochondrial homeostasis is one of the hallmarks of aging and disease in diverse species such as yeast and humans. In mammals, disruption of mitochondrial homeostasis is believed to be an underlying cause of aging and the etiology of numerous age-related diseases (de Moura et al., 2010; Figueiredo et al., 2009; Sahin et al., 2011; Schulz et al., 2007; Wallace et al., 2010). Despite its importance, there is still a great deal of controversy as to why age induces the disruption of mitochondrial homeostasis and how this process might be slowed or reversed.

In light of the foregoing, there is great need for novel compositions and methods for improving metabolism and mitochondrial function in aging tissues. Such compositions and methods would be useful for the treatment of age related and mitochondrial diseases, as well as for increasing stress resistance, improving resistance to hypoxia and extending the lifespan of organisms and cells.

NAD+ is an essential co-factor for several important enzymes (Canto and Auwerx, 2011). In mammals, NAD+ is generated from nicotinamide in a salvage pathway wherein nicotinamide phosphoribosyltransferase (NAMPT) converts nicotinamide to nicotinamide mononucleotide (NMN) which is then converted to NAD+ by nicotinamide mononucleotide adenylyltransferase (NMNAT) (Canto and Auwerx, 2011).

SUMMARY

As described herein, Hypoxia-Inducible Factor 1α (HIF-1α) interacts with the transcription factor c-Myc to inhibit c-Myc activity, causing genome asynchrony and the decline in mitochondrial function during aging. Reducing the ability of HIF-1α to inhibit c-Myc activity, such as by disrupting the formation of the complex containing HIF-1α and c-Myc, therefore conveys beneficial effects on metabolism, cellular fitness, survival (e.g., survival under hypoxic conditions) and mitochondrial function in aged tissues. Thus, agents that reduce inhibition of c-Myc activity by HIF-1α and/or disrupt the formation of a complex between HIF-1α and c-Myc (e.g., anti-HIF-1α antibodies, HIF-1α decoy proteins, small molecules), are useful for the treatment of age-related and mitochondrial diseases, including Alzheimer's disease, diabetes mellitus, heart disease, obesity, osteoporosis, Parkinson's disease and stroke. Such agents are also therefore useful for extending the life span, increasing the stress resistance and improving resistance to hypoxia of a subject (e.g., a human, a non-human animal and/or a plant) or a cell.

In certain embodiments, the instant invention relates to a method of treating or preventing an age-related disease